KRABs RegulaTE Gene Expression beyond the Embryo.

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Christopher J. Playfoot and Ian R. Adams *

MRC Human Genetics Unit, MRC Institute of Genetics and Molecular Medicine, University of Edinburgh, Western General Hospital, Crewe Road, Edinburgh, United Kingdom. EH4 2XU.

* Author for correspondence. Email: Ian.Adams@igmm.ed.ac.uk

Abstract

Transposable element (TE) silencing is initiated early in mammalian development and maintained during somatic differentiation. Reporting in this issue of *Developmental Cell*, Ecco *et al* (2016) show that in somatic tissues, TE regulation, and its subsequent effect on host gene transcription, is dynamic rather than locked in a silent state.

Main Text

Developmental biology involves a series of transitions between cell states that are determined by transcriptional networks controlling cell identity and function. These transcriptional networks do not only regulate genes, they also regulate some of the retroviral-derived transposable elements (TEs) that make up around 40% of mammalian genomes. However, there is growing evidence that TEs are not only responding to these transcriptional networks but are also contributing to them by influencing expression of host genes nearby (Chuong et al., 2013; Kunarso et al., 2010; Peaston et al., 2004). In this issue of *Developmental Cell*, Ecco *et al* (2016) show that TE silencing in differentiated somatic cells may be more dynamic than previously thought, and that programmed regulation of TEs could be contributing to host gene transcriptional networks during the development and maintenance of somatic tissues.

One of the major mechanisms that mammals use to regulate TEs involves the co-repressor KAP1 (TRIM28). KAP1 is targeted to specific genomic sequences, including TEs, by Krüppel-associated box zinc finger proteins (KRAB-ZFPs). KAP1 in turn recruits histone methyltransferases that induce the deposition of transcriptionally repressive H3K9me3 histone modifications at TE sequences (reviewed in Rowe and Trono, 2011). TE silencing has been proposed to be established early in development by KAP1, which induces repressive chromatin domains and DNA methylation that can then be maintained independently of KRAB-ZFP and KAP1 function in differentiated cells. Thus, the silencing of some

TEs in differentiated cells was thought to not require KRAB-ZFP and KAP1 activity (Rowe et al., 2010; Wolf et al., 2015). However, this mechanism was based on analysis of a relatively small number of TEs and KRAB-ZFPs and, given the number and diversity of TEs in mammalian genomes, it is not clear how universal this mechanism might be.

Using an elegant targeted GFP repression based functional screen of over 200 KRAB-ZFPs in somatic cell lines, Ecco *et al*. (2016) identified KRAB-ZFPs that recognize selected TE-derived sequences in the mouse genome. ChIPseq for ZFP932, one of these KRAB-ZFPs, and its paralog Gm15336 showed binding predominantly at KAP1 binding sites within distinct classes of TEs in embryonic stem (ES) cells. The authors deleted both KRAB-ZFPs by CRISPR/Cas9 genome editing in mouse ES cells, which led to reduced levels of KAP1 and H3K9me3 at target TE loci and transcriptional de-repression of these TEs, robustly demonstrating that these KRAB-ZFPs are targeting subsets of TEs for transcriptional silencing. Ecco *et al*. (2016) also noted that expression of ZFP932 and Gm15336 is relatively high in adult tissues compared to other KRAB-ZFPs expressed in ES cells and show in multiple somatic contexts that depletion of ZFP932/Gm15336 or KAP1 results in de-repression of KRAB-ZFP bound TEs. This de-repression is accompanied by reduced levels of repressive H3K9me3 but no changes in DNA methylation at these loci. Therefore, at least for some TEs, transcriptional repression in differentiating and terminally differentiated somatic cells is achieved through their persistent identification by KRAB-ZFPs and the continual recruitment of KAP1 (Figure 1).

Interestingly, Ecco et al. show that the de-repression of TEs that occurs in response to loss of ZFP932 and Gm15336 in mouse ES cells and somatic cells is accompanied by some changes in transcription of nearby genes. The ability of de-repressed TEs to affect transcription of nearby genes is a consequence of de-repressed TEs behaving as either promoters or enhancers, depending on the genomic context. Importantly, host gene transcripts that were driven by de-repressed TEs in ZFP932/Gm15338-depleted cells are present in some tissues that express low levels of these KRAB-ZFPs during normal development. Thus, developmental or physiological control of specific KRAB-ZFPs and KAP1 sub-complexes could be influencing transcriptional networks through programmed regulation of TEs (Figure 1). Given the widespread occurrence of TE-driven transcripts in mammalian transcriptomes, programmed regulation of specific subsets of TEs may be having a significant impact on the biology of their mammalian hosts, an impact that could provide many evolutionary benefits. Indeed, one somatic tissue which has been strongly associated with TE activity in recent years is the brain. The only autonomously mobile TE in the human genome, LINE-1, is expressed and mobilizes in neuronal cells. The consequent somatic mosaicism has been proposed to contribute to neuronal function (Coufal et al., 2009). It is possible that this expression of LINE-1 elements represents an example of developmentally programmed de-repression, and that LINE-1's effects on the transcriptional networks in this tissue are also contributing to neuronal

function. Similarly, some of the endogenous retrovirus (ERV) class of TEs are de-repressed in trophoblast stem cells and act as tissue-specific enhancers for core trophoblast developmental factors (Chuong et al., 2013). ERVs in humans are thought to be immobile and therefore have little mutagenic potential, yet are transcriptionally repressed by KAP1 in human ES cells (Turelli et al., 2014). Perhaps regulating potential effects on the expression of nearby genes is contributing to the evolutionary drive to recruit KAP1 to TEs.

One question that arises from the Ecco *et al.* (2016) study by is whether the developmentally programmed de-repression of TEs is providing new functions in somatic tissues. In the mouse germline, a TE-driven oocyte-specific isoform of the RNA endonuclease Dicer1 endows these cells with a unique hyperactive Dicer1 activity that is essential for oocyte development (Flemr et al., 2013). It will be of interest to determine if developmentally programmed de-repression of TEs induces expression of TE-driven genes that are imparting novel functions to somatic tissues.

Figure Legend

Figure 1. A role for KRAB-ZFPs in maintaining transposable element silencing in somatic tissues.

KRAB-ZFPs (ZFPs) initiate silencing of transposable elements (TEs) during early development by recruiting KAP1-dependent repressive chromatin modifications (black circles and squares) to these sites. For some TEs (brown), silencing in adult tissues can be maintained in the absence of KRAB-ZFPs/KAP1. Ecco *et al* (2016) show that some TEs (blue) require KRAB-ZFP/KAP1 to maintain their silencing in adult tissues, and that de-repression of these TEs can act as either ectopic enhancers (asterisk) or promoters (corner arrow) to stimulate transcription (wavy lines) of nearby genes. Programmed regulation of specific KRAB-ZFPs or KAP1 subcomplexes during development or in response to physiological stimuli can therefore influence host gene expression through repressing or de-repressing TEs.

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